Paper No. 27

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte VELI-MATTI LEHTOLA, EEVA-MARIA RANTALA, and PERTTI RANTALA

Appeal No. 2003-1376
Application No. 09/486,971

ON BRIEF

Before LIEBERMAN, ADAMS, and GRIMES, Administrative Patent Judges.

LIEBERMAN, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the decision of the examiner refusing to allow claims 1, 3, 4, 6, 11 and 14 through 19 which are all the claims pending in this application.

THE INVENTION

The invention is directed to a pharmaceutical composition comprising a pharmacologically acceptable salt of dichloromethylene biphosphonic acid and silicified

microcrystalline cellulose. Other embodiments of the invention are directed to a method for the manufacture of the aforesaid composition. Additional limitations are described in the following illustrative claims.

THE CLAIMS

Claims 1, 3, 11, and 15 are illustrative of appellants' invention and are reproduced below:

1. A tablet form of a pharmaceutical preparation comprising,

50 - 90% of a pharmacologically acceptable salt of dicholoromethylene biphosphonic acid as an active agent; and

5 - 25% of silicified microcrystalline cellulose.

3. The preparation according to claim 1, comprising:

a) from about 60 to 80% by weight of anhydrous disodium clodronate;

b) from about 8 to 20% by weight of silicified microcrystalline cellulose; and

c) from about 0.5 to 10% by weight of lubricants and/or disintegrants.

11. A pharmaceutical preparation, comprising,

a pharmaceutically acceptable salt of dicholoromethylene biphosphonic acid, and

an excipient, said excipient comprising silicified microcrystalline cellulose obtained by coprocessing microcrystalline cellulose with from about 0.1 to about 20% silicon dioxide, based on the amount of microcrystalline cellulose, to form an agglomerate of microcrystalline cellulose and silicon dioxide wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other and the silicon dioxide is integrated with the microcrystalline cellulose particles, but there is no chemical interaction between the two materials.

15. A method of manufacturing a pharmaceutical preparation according to claim 1, comprising:

mixing dry granules of a pharmacologically acceptable salt of dicholoromethylene biphosphonic acid with stearic acid;

sieving said granules;

mixing said granules with croscarmellose sodium, silicified microcrystalline cellulose and magnesium stearate to form a mixture;

forming tablets from said mixture in a tabletting apparatus;

and optionally coating said tablets with a coating solution.

THE REFERENCES OF RECORD

As evidence of obviousness, the examiner relies upon the following references:

Posti et al. (Posti)	5,525,354	Jun. 11, 1996
Sherwood et al. (Sherwood) (published World Intell. Prop. Org. Patent Application)	WO 96/21429	Jul. 18, 1996

Remington, Remington's Pharmaceutical Sciences, pp. 1319, 1325 (18th Ed., Mack Publ. Co., Easton, PA 1990)(hereinafter referred to as Remington's Pharmaceutical Sciences).

THE REJECTION

Claims 1, 3, 4, 6, 11, and 14 through 19 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Posti in view of Sherwood and Remington's Pharmaceutical Sciences.

OPINION

We have carefully considered all of the arguments advanced by the appellants and the examiner, and agree with the examiner that the rejection of the claims under Section

103(a) is well founded. Accordingly, we affirm the rejections for the reasons set forth in the Answer and the reasons discussed herein.

As an initial matter, it is the appellants' position that the claims are grouped as five separate and distinct groupings. Based upon the appellants' grouping of claims, we select claims 1, 3, 11, 15 and 16 as representative of the claimed subject matter and limit our consideration thereto. See 37 CFR §1.192(c)(7) (2002).

The Rejection under Section 103(a)

It is the appellants' position that the references do not suggest the claimed invention, Brief, page 4, and that there is, "no motivation to combine the . . . references," Brief, page 5. We disagree.

Posti is directed to a pharmaceutical composition containing a pharmaceutically acceptable salt of dichloromethylene biphosphonic acid, especially disodium clodronate. See column 1, lines 6-10. The pharmaceutical composition may be in the form of a tablet. See column 2, lines 1-3. We find that the amount of clodronate present in the composition is from 10 to 95% by weight. See column 2, lines 15-24. We find that the clodronate is combined with one or more additives including microcrystalline cellulose, colloidal sodium dioxide, croscarmellose sodium, magnesium stearate and stearic acid among a limited number of named additives. See column 3, lines 41-54. Furthermore, the utilization of these combined components is exemplified in Example 1. As noted by the examiner, Posti differs from the claimed subject matter in that there is no disclosure of coprocessing the microcrystalline cellulose and silicon dioxide. See Answer page 3.

To remedy this omission, the examiner relies upon a reference to Sherwood directed to, "a particulate agglomerate of coprocessed microcrystalline cellulose and from about 0.1% to about 20% silicon dioxide, by weight of the microcrystalline cellulose, the microcrystalline cellulose and silicon dioxide being in intimate association with each other." See page 9, lines 9-16. Sherwood discloses that although, "microcrystalline cellulose is generally considered to exhibit superior compressibility and disintegration properties," page 4, lines 16-18, there are numerous limitations resulting from the utilization of microcrystalline cellulose alone. See page 4, line 19 through page 5, line 27. As Sherwood explains with respect to the agglomerate of coprocessed microcrystalline cellulose and silicon dioxide, it is an object of the invention to prepare a solid drug dosage form, "which possesses excellent disintegration and dissolution properties when exposed, e.g., to gastrointestinal fluid." See page 9, lines 3-8. We find that Sherwood is directed to coprocessed microcrystalline cellulose and silicon dioxide compositions useful in wet and dry granulation methods. See page 10, lines 1-4. We find that the active ingredient and excipient may be directly compressed into a solid dosage. See page 10, lines 28-32. We find that the ratio of active ingredient to excipient is from about 1:99 to 99:1. See page 10, lines 21-22.

Based upon the above findings we conclude that it would have been obvious for the person having ordinary skill in the art to have substituted the coprocessed microcrystalline cellulose, silicon dioxide excipient of Sherwood for the separate microcrystalline cellulose and colloidal silicon dioxide of Posti.

As for the limitations of claim 3, the ratios disclosed by the combined teachings of Posti and Sherwood supra overlap those of claim 3 both with respect to the proportion of active ingredient, silicified microcrystalline cellulose and the presence of lubricants, i.e., component (c). We find, in this respect, the presence of stearic acid and magnesium stearate, both disclosed as lubricants, in Example 1 of Posti in an amount of about 2.5% by weight. Hence, the proportions required by claim 3 are met by the combined disclosure and teachings of Posti and Sherwood.

Similarly, the above findings disclose both the appropriate proportions and coprocessing of microcrystalline cellulose and silicon dioxide to provide components which are in intimate association with each other. In this respect, see also Sherwood, page 19, lines 2-30. Accordingly, no distinction is seen between the above disclosure and teachings and those required by claim 11.

Turning to claim 15 which additionally requires the presence of stearic acid, croscarmellose sodium and magnesium stearate, our findings supra indicated that each of these components were disclosed by Posti. As to the further requirements of claim 15 directed to sieving and tableting, we find that Sherwood discloses that dry screening of material containing an active ingredient in conjunction with the excipients may occur by using screens of from about 40 to about 200 mesh prior to tableting. See Sherwood, page 23, lines 29-33. We further find that Posti likewise discloses the techniques of sieving and

tableting. See Posti, Example 1. We conclude that the techniques of sieving and tableting required by the claimed subject matter are ordinary and routine in the art as disclosed by both Posti and Sherwood.

Finally as to claim 16, which further requires mixing the dry granules with an ethanolic solution of stearic acid, we find that Example 1 of Posti utilizes an ethanolic solution of stearic acid in preparing a clodronate tablet. Although, the ethanol solution of stearic acid is used in a mixing step having a sequence of mixing different from that present in claim 16, we conclude that ethanolic stearic acid is utilized as a routine component in the tableting process. The particular step at which the ethanolic solution is introduced is a matter within the skill of the art, there being no evidence of record to the contrary.

With respect to the claimed invention as a whole, the appellants argue that, "it is not obvious from the teachings of Sherwood and Posti, to prepare a clodronate preparation comprising SMCC that *does not require an enteric coating.*" See Brief, page 5. The claims in the record before us are directed to transitional language using the term, "comprising" and accordingly are open to the presence of additional components such as the enteric coating disclosed by Posti, disclosed by Sherwood, page 26 and claimed by the appellants, claim 15, as an optional embodiment. Accordingly, the presence or absence of an enteric coating fails to distinguish the claimed subject matter from the disclosure of the references of record.

The appellants further argue that Sherwood emphasizes and prefers the wet granulation method as opposed to Posti and the invention which are directed to dry granulation techniques. As we noted above however, Sherwood discloses, dry granulation, wet granulation and direct compression techniques. Even if the appellants were correct in their assessment that Sherwood prefers the utilization of a wet granulation technique, it is well settled however, that in a Section 103 inquiry, the teaching of a preferred specific embodiment is not controlling since the disclosure of the entire prior art including the non-preferred embodiments must be considered. See Merck & Co. v. Biocraft Labs., Inc., 874 F.2d 804, 807-08, 10 USPQ2d 1843, 1846 (Fed. Cir.), cert. denied, 493, U.S. 975 (1989). Inasmuch as the Sherwood reference as a whole discloses the dry mixing of the various components required for tableting an active pharmaceutical ingredient, the combination of the references would have been obvious to one of ordinary skill in the art.

Accordingly, we conclude that the combination of Posti and Sherwood is sufficient to establish a prima facie case of obviousness with respect to the claimed subject matter. As a rebuttal to the prima facie case of obviousness, appellants rely on the data present in a declaration to Posti, purported to provide evidence that the use of SMCC, silicified microcrystalline cellulose, improves the compressibility and friability of the resulting tablets. See Posti declaration, page 4. Having reviewed the data present, we conclude that appellants have not met their burden of showing unexpected results. In re Klosak, 455 F.2d 1077, 1080, 173 USPQ 14, 16 (CCPA 1972). It is not sufficient to assert that

the results obtained are unusual or unexpected. The burden of showing unexpected results rests on those who assert them.

The data presented in the declaration is directed to two comparisons, Batches 1 and 2, and Batches 3 and 4 respectively. Batches 3 and 4 are prepared according to the Posti patent. They contain a 1,000 mg tablet of disodium clodronate. Batch 3 contains 23.29 mg of SMCC as compared with Batch 4 which contains 22.83 mg of microcrystalline cellulose. We find that the minimum amount of SMCC required by the claimed subject matter to be present in the tableted composition is 5% according to claim 1. Inasmuch as 5% of 1,000 mg is 50 mg, the presence of only 23.29 mg of SMCC is outside the scope of the claimed subject matter. Accordingly, little, if any weight is accorded the results obtained both in terms of compressibility and friability percent. See the Table on page 4 of the declaration.

As to Batch 1 and 2 containing 1,000 mg of disodium clodronate, and 165 mg of SMCC, we determine that the single remaining comparison is not commensurate in scope with the claimed subject matter. Batch 1 within the scope of the claimed subject matter contain 165 mg or 16.5% SMCC. In contrast, the claimed subject matter permits the presence of 5 to 25% of SMCC. Accordingly, it cannot be concluded that the results obtained with a 16.5% SMCC would be similar if the composition contained only 5% SMCC. Furthermore, the data presented are directed to an SMCC composition containing 2% of silicon dioxide. In contrast, claim 11 defines coprocessed SMCC as containing 0.1 to about 20% silicon dioxide. It is not seen that the utilization of SMCC containing 2%

silicon dioxide is necessarily reflective of a composition containing either 0.1% of silicon dioxide or 20% silicon dioxide. Furthermore, the data presented are directed to SMCC compared with a mixture of microcrystalline cellulose and colloidal anhydrous silicon dioxide. Neither the form of silicon dioxide nor the particle size utilized in the preparation of SMCC is explicitly disclosed. Accordingly, we conclude that no evidence of unobvious or unexpected results, may be drawn from the single comparison present in the Posti declaration. We further conclude that the data present in the Posti declaration are not commensurate in scope with the degree of protection sought by the claimed subject matter. See In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 778 (Fed. Cir. 1983); In re Tiffin, 448. F.2d 791, 792, 171 USPQ 294, 294 (CCPA 1971). It is well settled that "objective evidence of nonobviousness must be commensurate in scope with the claims." In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); In re Dill, 604 F.2d 1356, 1361, 202 USPQ 805, 808 (CCPA 1979) ("The evidence presented to rebut a prima facie case of obviousness must be commensurate in scope with the claims to which it pertains.")

Finally, the Posti declaration concludes that the data present in terms of crushing strength and friability, "demonstrate the advantageous properties of SMCC regarding compressibility of the powder mass, and friability of the resulting tablets." See Posti declaration, page 4. These physical characteristics however are precisely the same physical characteristics disclosed by Sherwood as constituting the motivation for substituting the coprocessed SMCC for microcrystalline cellulose. See Sherwood, Abstract, page 9, lines

3-8, and page 11, lines 25-30. Accordingly, the results obtained by appellants, in our view, are expected beneficial results which are evidence of obviousness, just as unexpected results are evidence of unobviousness. In re Gershon, 372 F.2d 535, 537, 152 USPQ 602, 604 (CCPA 1967).

Based upon the above reasons and those set forth in the Answer, we have determined that the examiner has established a prima facie case of obviousness. Upon reconsideration of all the evidence and argument submitted by appellants, we have determined from the totality of the record that the preponderance of the evidence weighs in favor of obviousness within the meaning of 35 U.S.C. § 103. See In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Accordingly, the decision of the examiner is sustained.

A discussion of Remington's Pharmaceutical Sciences is not needed in reaching our decision.

DECISION

The rejection of claims 1, 3, 4, 6, 11, and 14 through 19 under 35 U.S.C. §103(a) as being unpatentable over Posti in view of Sherwood and Remington's Pharmaceutical Sciences is affirmed.

The decision of the examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

PAUL LIEBERMAN
Administrative Patent Judge

DONALD E. ADAMS
Administrative Patent Judge

ERIC GRIMES
Administrative Patent Judge

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